April 16, 2002

MEMORANDUM

SUBJECT: Atrazine: Response to Public Comments on the EPA's January 19, 2001 Revised Preliminary Human Health Risk Assessment and Associated Documents for the Reregistration Eligibility Decision (RED). PC Code: 080803. DP Barcode: D282037

FROM: Catherine Eiden, Branch Senior Scientist
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TO: Kimberly Lowe, Chemical Review Manager
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Please find attached the response document to public comments on the EPA's January 19, 2001, "Atrazine: HED's Revised Preliminary Human Health Risk Assessment (and Associated Documents) for the Reregistration Eligibility Decision (RED). HED responders included: Catherine Eiden, Vicki Dellarco, and Linda Taylor.

Background

This memorandum contains HED's responses to public comments submitted during the 60-day public comment period for "Atrazine. HED's Revised Preliminary Human Health Risk Assessment, January 19, 2001". The HED received 26 sets of comments from citizens, consultants, and groups representing the agribusiness and the farming community. Those individuals and groups are listed below:

The Texas Farm Bureau, Illinois Fertilizer and Chemical Association, Missouri Ag Industries Council, Inc., Florida Farm Bureau Federation, Georgia Agribusiness Council, Bruce & Ella Kelsey, National Corn Growers Association, Iowa Farm Bureau Federation, U.S. Sugar Corporation, Western Growers Association, National Grain Sorghum Producers, Missouri Corn Growers Association, Texas Grain Sorghum Association, Kentucky Fertilizer and Agricultural Chemicals Association, Missouri Soybean Association, Russel R. Weisensel, American Farm Bureau Federation, Kentucky Corn Growers Association, Ohio Farm Bureau Federation, Illinois Farm Bureau, Steve Hoak, Glades Crop Care, Inc., Triazine Network, American Crop Protection Association, Consultants in Toxicology, Risk Assessment, and Product Safety, Sugarcane Growers Cooperative of Florida, and the Weed Science Society of America.

The HED also received comments from 8 non-profit organizations (environmental groups) representing public concerns. Those groups are listed below:

Breast Cancer Action Network (BCA), Natural Resources Defense Council (NRDC), Pesticide Action Network of North America (PANNA), Northwest Coalition for Alternatives to Pesticides, Beyond Pesticides, Environmental working Group, Consumer’s Union, and World Wildlife Fund.

Most of the comments from the first group listed above representing the farming community related to the same issues. HED has provided responses to those issues/comments that were common to these groups rather than providing individual responses to each of the comments . Responses to farming community concerns are presented first. Many of the issues and concerns expressed were common to the non-profit community, as well. Therefore, as above, HED has presented responses to those issues/comments that were common to these groups rather than providing individual responses to each of the comments . Responses to the environmental community are presented second.

Farming Community Concerns:

<u>Comment</u>

Most of the comments commended the EPA for determining that atrazine is not a likely human carcinogen. There were a few comments reflecting confusion about the Agency's determination of atrazine's carcinogenic potential.

HED Response
The Agency's Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP), convened in June 2000, determined that the mode of action for the carcinogenic potential in the Sprague-Dawley rat is not likely to be operative in humans. HED's Cancer Assessment Review Committee (CARC) concurred with the SAP, also concluding that the mode of action is not relevant to humans. This conclusion was based on the following considerations: though hypothalamic disruption of pituitary function (i.e., attenuation of the LH surge) and resulting estrous cycle disruption may be occurring in humans following atrazine exposure, the hormonal environment resulting from these events would be expected to be much different from the hormonal environment seen in the rat. The prolonged/increased exposure to estrogen and prolactin as seen in the rat would not be expected to occur in humans. The prolonged/increased exposure to estrogen and prolactin in the rat is the basis of early-onset and increased mammary tumors in susceptible strains of rats. Additionally, the mutagenicity database is quite extensive and indicates that atrazine is not mutagenic. Consequently, in accordance with the *1999 Draft Guidelines for Carcinogen Risk Assessment*, the CARC classified atrazine "not likely to be carcinogenic to humans". Therefore, a cancer risk assessment was not conducted for atrazine. HED acknowledges the comments' general agreement with the Agency's determination that atrazine is not a likely carcinogen in humans.

Hopefully, the paragraph above clarifies the issue. The point is that although the mechanism of carcinogenesis in the rat attributed to atrazine is not likely to be operative in humans, hypothalamic disruption of pituitary function (i.e., attenuation of the LH surge) and resulting estrous cycle disruption may be occurring in humans following atrazine exposure.

Comment
"EPA should not be using an endpoint for the preliminary risk assessment based on studies conducted with the Sprague-Dawley rat when the Scientific Advisory Panel (SAP) has determined that the mode of action in this particular strain of rat is not relevant to humans. Use of this endpoint and inappropriate methodology (deterministic) pinpoints 28 community water systems considered to have less than a 1000-fold margin of safety for atrazine levels, thus exceeding EPA's level of concern. When correct methodology and endpoints are used, a safety margin of greater than 1000-fold exists in all exposure scenarios. The Agency has agreed to conduct a probabilistic assessment. Why could this not have been accomplished prior to publishing the preliminary risk assessment on the website?" In general this issue is part of all of the submitted comments from the groups listed above, and makes the point that EPA has used incorrect endpoints and methodologies in the preliminary risk assessment.

HED Response

The Endpoint Used in the Preliminary Risk Assessment:
Atrazine alters hypothalamic gonadotrophin releasing hormone (GnRH) release in rats. There are also some data that indicate that atrazine diminishes norepinephrine in the rat hypothalamus as an initial or early site of action which in turn leads to diminished GnRH release. Atrazine also increases dopamine levels which can result in a diminished pituitary secretion of prolactin.

Therefore, atrazine appears to operate at the level of the hypothalamus. In both humans and rats, hypothalamic GnRH controls pituitary hormone secretion (*e.g.,* luteinizing hormone (LH), and prolactin (PRL). The hypothalamic-pituitary axis is involved in the development of the reproductive system, and its maintenance and functioning in adulthood. Additionally, reproductive hormones modulate the function of numerous other metabolic processes (*i.e.,* bone formation, and immune, cental nervous system (CNS) and cardiovascular functions). Therefore, altered hypothalamic-pituitary function can potentially broadly affect an individual's functional status and lead to a variety of health consequences.

The report of the Scientific Advisory Panel (SAP) convened in June 2000 to consider these health consequences of exposure to atrazine, indicated that "*..it is not unreasonable to expect that atrazine might cause adverse effects on hypothalamic-pituitary function in humans*." Therefore, atrazine's effect on ovarian cycling and the pre-ovulatory LH surge (as well as its effects on pregnancy, puberty, suckling induced PRL release which leads to prostatitis) are viewed as neuroendocrinopathies or biomarkers indicative of atrazine's ability to alter hypothalamic-pituitary function in general across species. It should be noted that atrazine's neuroendocrine effects have been demonstrated in several strains of rats (SD, Long Evans, and Wistar).

Attenuation of the luteinizing hormone (LH) surge, considered a biomarker indicative of atrazine's ability to alter hypothalamic-pituitary function, and estrous cycle disruptions demonstrated in female rats (e.g.,Sprague-Dawley and Long Evans) is the basis of the chronic reference dose (cRfD) of 0.018 mg/kg/day, and is used to assess risks associated with chronic dietary exposures, intermediate-term, and long-term oral incidental, dermal, and inhalation exposures. Alteration of the hypothalamic-pituitary function as evidenced through the attenuation of the LH surge was dose-dependent and observed between 1 to 5 months of daily dosing in a 6 month study, making this endpoint an appropriate endpoint to assess intermediate-term (30 days to several months) and chronic (several months to lifetime) exposures to atrazine. Although this specific effect (attenuation of the LH surge) is operative in females, it was selected as the basis for intermediate-term and chronic risk assessment for all population subgroups, because it is the most sensitive endpoint available from the toxicity database and therefore protective of other adverse effects, and it is indicative of alterations of the hypothalamic/pituitary/gonadal axis, which may occur in the offspring and adults of other species (humans).

The point is that although the mechanism of carcinogenesis in the rat attributed to atrazine is not operative in humans, hypothalamic disruption of pituitary function (i.e., attenuation of the LH surge) and resulting estrous cycle disruption may be occurring in humans following atrazine exposure. It is this possibility of hypothalamic disruption of pituitary function that forms the basis of the intermediate-term and chronic risk assessments.

Methodology Used in the Preliminary Risk Assessment:
Several comments express concern that the methodologies used in the preliminary risk assessment are inappropriate, specifically, because they are deterministic rather than

probabilistic. HED agrees that a probabilistic assessment of exposures to atrazine in drinking water is the preferred approach. To date, HED has conducted drinking water exposure assessments for pesticides using screening-level water quality models for the most part. However, there are more monitoring data available to assess exposures to atrazine in finished drinking than for any other pesticide. For this reason, monitoring data on actual residues of atrazine in finished drinking water have been used for this assessment in lieu of the screening-level water quality models usually employed. Because of the volume of information available through various data sets for thousands of community water systems and hundreds of rural wells, HED has developed a methodology by which the data have been used initially in a deterministic assessment of exposure. Community water systems identified under the deterministic approach as having exposures above HED's level of concern, will be assessed under a probabilistic approach making use of all distributions of data available on drinking water consumption, body weight, and total chlorotriazine concentrations in finished drinking water. Because of the time constraints on this risk assessment, this document contains only the results of the deterministic assessment of drinking water exposure for atrazine. Future revisions to the drinking water exposure assessment will include probabilistic assessments of drinking water exposure for those community water systems found to have concentrations of total chlorotriazine concentrations above HED's level of concern under the deterministic assessment presented in this document

HED agrees that a probabilistic methodology is more robust than the methodology used under the deterministic assessment, and has encouraged Syngenta to provide a probabilistic assessment for the CWS identified under the deterministic approach using data combined across data sets for specific CWS, and time-weighted chlorotriazine concentrations.

Comment

"The proposed imposition in the current preliminary risk assessment of an extra 10-fold safety factor in addition to the standard 100-fold safety factor is unreasonable and unwarranted. It appears that EPA used excessive doses and forced feeding to reach "potential" adverse effects in the special development studies with rats. Since all new data indicate that children are actually 3.5 times less sensitive to atrazine than adults, the 100-fold safety factor provides ample protection." In general, all of the above comments raised the issue of the additional 10-fold safety factor for infants and children as applied to the risk assessment as unwarranted.

HED Response

The decision to apply a 10X FQPA safety factor was based on several sources of residual concerns and uncertainty associated with exposures to the chlorotriazines. These sources of uncertainty primarily concern the hazard of atrazine and it metabolites, although there are some residual concerns in exposure database. Although the FQPA safety factor should not be parceled out among the varying concerns, but rather the concerns cited considered *in toto* and used as the basis for retaining the default FQPA safety factor, the FQPA 10X for atrazine results from a 3X uncertainty factor for hazard-based concerns and a 3X uncertainty factor for exposure-based concerns.

The decision to retain the default 10X FQPA safety factor or to assign a different safety factor is informed by the conclusions presented in the risk characterization, i.e., the final step in the risk assessment process. The risk characterization is an integration step wherein the weight-of-evidence analyses for the completeness of the toxicity database, the degree of concern for pre- and postnatal toxicity, and results of the exposure assessments are combined to evaluate whether the presumptive 10X safety factor should be retained. If there is a high level of confidence that the combination of the hazard and exposure assessments is adequately protective of infants and children, then the presumption in favor of the additional 10X default FQPA safety factor would be obviated and the FQPA safety factor is reduced to 1X. Conversely, if there is evidence that raises concern for pre- or postnatal toxicity or problems with the completeness of the toxicity or exposure databases and these uncertainties have not been adequately dealt with in the toxicity and/or exposure assessments (through use of traditional uncertainty factors or conservative exposure assumptions) then the presumptive additional 10X safety factor should be retained (see "Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Reassessment", Office of Pesticide programs, US EPA, January 31, 2002 (http://www.epa.gov/pesticides/trac/science/#10-fold).

Scientific judgment should be used in determining the appropriate size of the FQPA safety factor based on the toxicology and exposure data available for the pesticide and based on the understanding of whether the missing or inadequate data on a pesticide are likely impact to impact the risk assessment, for example by identifying new effects and effects occurring at lower doses. In the case of atrazine and its metabolites a major consideration on the toxicology side was how thorough were the data with respect to life stage and end point assessment. There was no information on atrazine concerning dosing that covered all critical developmental periods, gestation through puberty in both male and female rats, in particular dosing early in development. Such exposure might reasonably be anticipated to lead to lower NOAELs than those identified in the current studies.

Furthermore, atrazine's effects on neurotransmitters/peptides were only evaluated after acute dosing and thus there were residual concerns for longer exposures and longer doses to atrazine and its metabolites and their impact on these neurotransmitters and peptides that are known to be critical for development and normal functioning. Also, atrazine and its metabolites have not been evaluated for CNS effects, and thus there were residual concerns of whether atrazine's CNS mode of action would lead to behavioral effects in the young, and at what dose compared to its reproductive developmental effects.

It is important to note that in the case of atrazine, there are more reliable data on actual exposures to chlorotriazines in finished drinking water than for any other pesticide. In this sense, the exposure database for atrazine is particularly robust. As a result we have moderate to high confidence and there is less uncertainty in our estimates of exposure to the chlorotriazines in drinking water than for all other pesticides assessed to date. However, because of the infrequency of monitoring under the SDWA, and because data on the chlorotriazine degradates in surface water and groundwater (rural wells) are limited to a few CWS and/or wells and have been extrapolated to other CWS, i.e., data are not available for each CWS assessed as are data on

the parent compound, atrazine, there is residual uncertainty regarding the full extent of exposures to atrazine in drinking water.

In total, these residual concerns led to the decision to retain the 10X FQPA factor. An order of magnitude beyond the standard uncertainty factors (100X) is considered adequately protective of all populations including children. It is unlikely that new effects that may be potentially identified would result in NOAELs lower than an order of magnitude from the current NOAELs. Given the existing monitoring database, it is also unlikely that high-end exposures an order of magnitude greater than those already identified exist. Therefore, 10X factor is believed to be adequate given the overall toxicity database and exposure information available for atrazine and the chlorodegradates. Thus, HED believes the decision to apply a 10X FQPA safety factor is justified and adequately protective. In response to these uncertainties, the additional 10-fold safety factor for children has been applied, and studies examining CNS alterations have been recommended

Comment

"We assume the chronic assessment is based on very long term or lifetime exposures in laboratory feeding trials. We must therefore, ask if it is appropriate to use a single short-term "seasonal" drinking water exposure as a basis for chronic assessments. Seasonal data represent only a small portion of a normal life expectancy (3 month data reflect less than 0.5% of a 70-year lifespan). Chronic exposure estimates based on mean annual data would be better even though they also represent a relatively short time period (less than 2% of a 70-year lifespan)."

We would also like to know the frequency with which individual sites exceed level of concern. It is not unreasonable to average a site's 5-year SDWA monitoring data.

HED Response

There has been confusion in the public comments and on the part of the registrant regarding the endpoint used to assess intermediate-term and chronic exposures to atrazine in drinking water. As stated above, attenuation of the luteinizing hormone (LH) surge, considered a biomarker indicative of atrazine's ability to alter hypothalamic-pituitary function based on estrous cycle disruptions demonstrated in female rats (e.g.,Sprague-Dawley and Long Evans), is the basis of the chronic reference dose (cRfD). It is used to assess risks associated with chronic dietary exposures, intermediate-term, and long-term oral incidental, dermal, and inhalation exposures. Alteration of the hypothalamic-pituitary function as evidenced through the attenuation of the LH surge is dose-dependent and has been observed between 4 to 5 months of daily dosing in a 6 month study in the rat, and between 3 and 30 days depending on dose in shorter-term studies. Consequently, OPP's Hazard Identification Assessment Review Committee (HIARC) concluded that this endpoint is an appropriate endpoint to assess intermediate-term (30 days to 6 months) and chronic (6 months to lifetime) exposures to atrazine, which are particularly relevant for assessing seasonal pulses of atrazine coursing through drinking water systems. Traditionally, the 6 month study is not considered a lifetime study, but a subchronic study. However, it was considered appropriate to assess chronic (more than 6 months) as well as intermediate-term (30

days to 6 months) exposures to atrazine, because the endocrine effect selected from this study as the basis of intermediate-term and chronic risk assessments (attenuation of the LH surge) normally occurs in aging Sprague-Dawley rats at about 9 months of age. Consequently, a study of longer duration (12 months to 2 years) to assess this endpoint would be of limited value.

This endpoint is particularly appropriate for assessing intermediate-term and chronic exposures to atrazine in drinking water, as these exposures occur both as seasonal pulses from weeks to months in duration, and chronically from months to years in duration, reflective of atrazine's use patterns and occurrence in drinking water.

The use of a long-term average concentration value as from a period mean spanning 5 year's of data would be more appropriate for use in an exposure assessment of lifetime exposures, such as, for carcinogenic effects. However, as atrazine is no longer considered a likely human carcinogen, long-term multi-year exposures to atrazine were not considered. There were only a few community water systems (CWS) with annual average and seasonal average total chlorotriazine concentrations exceeding HED's level of concern in more than 1 year. They were: Hettick, Shipman, Salem, Palmyra-Modesto, and ADGPTV all in Illinois, and Dearborn in Missouri. The Shipman reservoir has been removed as a drinking water source. The names of those CWS can be found in the risk assessment document available on OPP's website.

Comment

Most comments expressed concern that EPA did not use accurate and representative characterizations of products containing atrazine, scientifically defensible interpretation of the available valid and reliable toxicological studies, statistically sound interpretation of residue concentrations of atrazine and its metabolites in surface water and groundwater community water supplies (CWS); and, incorporation of probabilistic risk assessment methods to better understand and evaluate drinking water post application exposures to atrazine and its metabolites.

HED Response

Although the commentary did not specify what each of their particular concerns were, taking each of these concerns individually, HED assumes that regarding the characterization of products containing atrazine, the commentary believe that erroneous assumptions about use rates, and acres treated were used in the occupational and residential risk assessments. HED has tried to obtain the most current information on use rates as proscribed on product labels for use in risk assessments. Likewise, HED has tried to obtain the most current information on maximum and typical acres treated with a product on a specific use site, and include these in risk assessments. Because labels to proscribe a maximum rate, this rate must be included in any risk assessment even if it does not represent typical rates. The risk estimates are intended to be conservative, but reasonable.

As to scientifically defensible interpretation of the available valid and reliable toxicological

studies, HED assumes the commentary believe that inappropriate endpoints were selected for use in risk assessment. HED defers to the response given under the comment above regarding endpoint selection.

As to concerns expressed regarding statistically sound interpretation of residue concentrations of atrazine and its metabolites in surface water and groundwater community water supplies (CWS), HED notes that this comment probably relates to the methodology used in the risk assessment to estimate total chlorotriazine concentrations as annual or seasonal means in CWS using surface water. The methodology used by the OPP differs from that proposed and used by Syngenta. HED believes the point is not who estimated the "correct" value, because the exact value cannot be known with certainty unless daily samples were taken during the period for which an average was estimated. Although there are differences in the annual and seasonal averages estimated by the EFED and Syngenta, the differences are on the order of a few ppb for most CWS, or at most 2X for a few CWS. HED has included the concentration values calculated by Syngenta using time-weighting in the risk assessment (table 1 of Attachment 4 of Syngenta's comments). Although HED concedes that Syngenta's approach of time-weighting is more scientifically valid, the approach used by OPP and that by Syngenta are reasonable for a screening assessment. The end result of the methodology used by the Agency was to identify CWS under a deterministic screening assessment for inclusion in probabilistic assessments. The methodology preferred by Syngenta for estimating total annual and seasonal chlorotriazine concentrations has been used in these probabilistic assessments. Therefore, HED believes it is of little value in reanalyzing total annual and seasonal chlorotriazine concentrations using the time-weighting methodology. Given the uncertainty surrounding any estimate of annual or seasonal average concentration values, HED has edited the drinking water exposure and risk assessment portion of the revised preliminary risk assessment to clarify that under the deterministic approach and methodologies used, seasonal or annual mean concentrations are estimates, and that any individual's exposure approaching, equal to, or above a level of concern is potential. More specific details on HED's response to this issue as raised by the registrant can be found in HED's response to Syngenta's comments contained in the memorandum dated April 16, 2002, D282042, C. Eiden.

As to concerns raised regarding incorporation of probabilistic risk assessment methods to better understand and evaluate drinking water post application exposures to atrazine and its metabolites, HED has reviewed Syngenta's probabilistic assessment of total chlorotriazine concentrations in 28 CWS identified as candidates for probabilistic assessment. The results of that review are also contained in the memorandum dated April 16, 2002, D278468. In addition, HED had concerns with the methodology used by Syngenta in that probabilistic assessment.

Although the methodology used by Syngenta to assess exposure to chlorotriazine residues in drinking water probabilistically results in more refined estimates of exposure and risk for the 28 CWS assessed than the deterministic approach used in the revised preliminary risk assessment, depending on which percentile of exposure is selected as the basis of the risk estimate, the improvement in the risk estimates is limited to only a few CWS. HED recommends the assessment for the 28 CWS be conducted using the methodology currently approved/used by OPP for cumulative dietary exposure assessment. This is OPP's preferred approach.

Specifically, the exposure assessment should include: 1) rolling sequential 90-day exposure periods (90 consecutive days for a given year) across the entire 1993 to 2000 data set of chlorotriazine concentrations in finished drinking water for each CWS, 2) separate assessments for male and female adults, and 3) more recent consumption data from the USDA's Continuing Survey of Food Intake by Individuals (CSFII 1994 to 1996). The preferred methodology should allow sequential daily chlorotriazine concentration values for rolling 90-day periods to be randomly matched with daily consumption values that also vary daily over the rolling 90-day periods for an individual as per CSFII records. This approach to the assessment maximizes randomness and variability, and should result in the most refined estimates of exposure using the available data.

As a result, Syngenta is conducting another probabilistic assessment in line with OPP's preferred methodology for probabilistic risk assessment to provide a more refined estimate of exposures to chlorotriazines in drinking water. The results will be included in the final risk assessment.

Environmental Community Concerns:

Comment

Atrazine's cancer classification:

All of the comments expressed concern that the Agency's determination that atrazine was "not likely to be a human carcinogen" was premature. The comments argue that this decision was based on the fact that the mode of action leading to increased incidence and early-onset of mammary adenoma/carcinomas in the Sprague-Dawley rat is not operative in humans, but appears to rule out any other mode of endocrine-mediated mode of action leading to cancer in humans. They also comment that there is a weight-of-evidence suggestive of atrazine-linked cancer in the ovaries, breasts and prostate based on broad endocrine disruption, and cite epidemiological studies as evidence, as well as an article by A. Pinter, et al, 1990. They call for more testing to elucidate these effects, and to maintain the cancer classification until more data are available to rule out other cancers as a result of atrazine exposures. Finally, the comment is made that the International Agency for Research on Carcinogens (IARC) came to a different conclusion than EPA. IARC concluded that there is inadequate evidence in humans for the carcinogenicity of atrazine, but sufficient evidence in experimental animals.

HED Response

Contained in this complex comment are concerns about atrazine's cancer classification, epidemiology study results and a citation of Pinter et al. (1990) as further evidence of atrazine's carcinogenic potential, and its' endocrine effects. Responses to each of these concerns will be taken in the order given above.

Cancer Classification:

Regarding the carcinogenic classification of atrazine, EPA agrees with the SAP comments as well as IARC. IARC indicated in their 1999 report that "There are critical interspecies differences in hormonal changes associated with reproductive senescence. Therefore, there is

strong evidence that the mechanism by which atrazine increases the incidence of mammary gland tumors ins Sprague-Dawley rats is not relevant to humans." The FIFRA SAP also stated, "there are considerable differences between hypothalamic-pituitary-ovarian function in rats and humans, and the effects of aging on the function of the axis also is quite dissimilar. Therefore, it is unlikely that the mechanism by which atrazine induces mammary tumors in female SD rats could be operational in humans." It should be further noted that carcinogenicity testing in other strains of rat and mice did not result in treatment-related increases in incidences of tumors when compared to controls. Therefore, EPA's conclusion that atrazine's cancer mode of action is not likely to be operative in humans, and thus should be classified as "not likely to be carcinogenic to humans" is consistent with both IARC and SAP. Therefore, in light of the current toxicological evidence as presented before the Scientific Advisory Panel (SAP) in June 2000, this endpoint is no longer relevant to humans and cannot be used to quantitate a cancer risk for humans from exposures to atrazine.

Epidemiologic Studies:
One Panel member [SAP] suggested that atrazine be classified as a "possible human carcinogen" given the positive evidence from the occupational epidemiologic studies. However, when taken together, the epidemiological evidence is inconclusive and the evidence from occupational studies could be outweighed by the fact that environmental exposures to atrazine would be lower than the exposures occurring in an occupational setting. The epidemiological evidence is insufficient to raise a cancer concern.

OPP has reviewed many epidemiological studies on atrazine. These studies deal with various cancers of the ovary, prostate, colon, breast, leukemia, non-Hodgkin's lymphoma. The results of these reviews can be found in their entirety in the following memoranda: "Review of Atrazine Incident Reports", DP Barcode: D270014, "Review of five epidemiological published articles for SAP", DP Barcode: D262405, and "A Follow-up Study of Mortality Among Workers at the Novartis St. Gabriel Plant & Follow-up Study of Cancer Incidence Among Workers in Triazine-Related Operations at the St. Gabriel Plant, DP Barcode: D281568 & D278933. The studies reviewed are: IARC Overall Evaluation of Carcinogenicity to Humans, "A Follow-up Study of Workers at the Ciba-Geigy St. Gabriel Plant", E. Delzell, et al, April 8, 1996, "Atrazine, An Epidemiological Study at the Schweizerhalle Plant", R. Gass et al., January 15, 1993, Ciba Geigy Herbicide Mortality Study, "Ovarian Mesothelial Tumors and Herbicides: A Case-Control Study", Donna, et al., 1984, "Triazine Herbicides and Ovarian Epithelial Neoplasms, Donna, et al., 1989, "Agricultural Herbicide Use and Risk of Lymphoma and Soft-Tissue Sarcoma", Hoar, et al., 1986, "Pesticide Exposures and Other Agricultural Risk Factors for Leukemia Among Men in Iowa and Minnesota", Brown, et al., 1990, "Herbicides and Colon Cancer, Hoar, et al., 1985, "A Case-Control Study of Non-Hodgkin's Lymphoma and Agricultural Factors in Eastern Nebraska, Zahm, et al., 1988, "Farming and Non-Hodgkin's Lymphoma, Cantor, et al., 1985, "Role of the Herbicide Atrazine in the Development of Non-Hodgkin's Lymphoma ", Zahm, et al., 1993, "Triazine Herbicide Exposure and Breast Cancer Incidence: An Ecological Study of Kentucky Counties", Kettles, et al., 1997, and "Correlation Analysis of Pesticide use Data and Cancer Incidence Rates in California Counties", Mills, et al., 1998.

In summary, reviews of the epidemiological studies dealing with prostate cancers and exposure to atrazine conclude that the increases in prostate cancers among workers manufacturing atrazine are attributable to the increased PSA screening conducted at the plants as a part of routine check-ups at the plants, and could not be conclusively linked to atrazine exposure. The reviews of studies dealing with non-Hodgkin's lymphoma (NHL) concluded that there was little to no increase in the risk of NHL attributable to the agricultural use of atrazine after adjustment for the use of other pesticides, specifically 2,4-D and organophosphates. Or put another way, there is little evidence that atrazine exposure explains any appreciable increase in NHL over the last 15 years in the US. Reviews of studies dealing with ovarian cancers conclude that definite exposure to triazines was associated with a 2 to 3-fold increase of borderline significance in the risk for ovarian cancer, but that confirmatory studies were needed as this study was small and potentially confounded by exposure to other herbicides, which was not controlled for in this study. Reviews of studies for leukemia conclude that the results for an association between leukemia and atrazine are unremarkable. Reviews of studies on breast cancers show only modest increases in risk that are in the same range as non-chemical risk factors not measured. The reviews conclude that in general, epidemiological studies containing information on atrazine exposures and cancer either indicate no significant increases in cancer risk that is directly associated with atrazine exposure, or raise more questions than they answer.

OPP concludes that "the results of the human epidemiology studies do not provide clear evidence of an association between triazines and cancer. Some of the studies, particularly those in which hormone-responsive cancers such as breast, ovary and prostate, were examined, are suggestive of a possible association. There is also suggestive evidence of a possible association of triazine exposure and NHL. Further epidemiologic research is needed - especially in the area of hormone-responsive cancers" (Final Report - Atrazine: Hazard and Dose-Response Assessment and Characterization, Part B- Hazard Assessment and Review of Available Studies, report prepared for June 2000 SAP or www.epa.gov/scipoly/sap/2000/index.htm#June 27). OPP recommends that the commentary consider the communities using drinking water from the community water systems identified in the risk assessment as excellent sites for future epidemiologic studies on atrazine exposures. Clearly, these are some of the communities receiving the highest atrazine exposures via drinking water.

Pinter et al. (1990):
The comments cite the Pinter et al. (1990) study as further evidence of atrazine's carcinogenicity. This study has been reviewed by OPP. The study showed lack of carcinogenic effect in female F-344 rats, but did find increased incidence of benign mammary tumors in male F-344 rats when high dose males were compared to low dose males. Normally, tumor incidence is compared between treated and control (untreated) animals. However, in this study, which was a lifetime study, the high-dose animals with the reported increase in benign mammary tumors lived significantly longer than the control and low-dose animals, i.e., there were no control animals remaining alive at the end of the study to compare with treated animals. OPP concluded that based on historical control data for aging male F-344 rats from typical two-year bioassay studies, the study authors did not make the case that the increase in male benign mammary tumors was because of atrazine exposure, and that the tumors appearing in the high-dose males

did not appear to be found at a rate any higher than what would be expected for untreated F-344 males of comparable age. A discussion of Pinter, et al. (1990) can be found in "Hazard Assessment and Review of Available Studies [Part B] of the May 22, Preliminary Draft Hazard and Dose-Response Assessment and Characterization" - Atrazine, FIFRA Scientific Advisory panel (SAP) June, 2000 (see http://www.epa.gov/scipoly/sap/2000/june27/finalparta_atz.pdf).

Endocrine Effects:
EPA is clearly concerned about other modes of action and effects on the central nervous system (CNS) and endocrine systems, and has required further testing on atrazine. Although early onset of mammary adenomas and carcinomas have only been ascribed to the Sprage-Dawley (SD) rat, endocrine effects have been seen in a number of species as noted by the comments. Although atrazine's neuroendocrine mode of action is not likely to produce cancer in humans the SAP did indicate that "nevertheless, it is not unreasonable to expect that atrazine might cause adverse effects on hypothalamic-pituitary function in humans". Therefore, this does not specifically rule out potential non-cancer effects. Therefore, HED selected the depression of the luteinizing hormone surge in the female SD rat as a biomarker indicative of neuroendocrineopathies potentially occurring in humans, including children as the most significant endpoint in the toxicity database for atrazine for such effects, and was used as the basis of the human health risk assessment. This endpoint was also the most sensitive endpoint in the toxicity database for atrazine, and is considered protective.

Comment

FQPA Safety Factor:
EPA should use an additional FQPA safety factor of 30X in the human health risk assessment for atrazine. Although the additional 10X FQPA safety factor applied in the current assessment is appropriate, it does not go far enough to provide protection given the uncertainties surrounding the toxicity of atrazine. The comments argue that data gaps for toxicity and water monitoring data for degradates alone merits an additional 10X safety factor, and that the quantitative increased susceptibility of infants and children to prostate effects as a result of DACT exposures merit an additional 3X safety factor. In effect, the endocrine effects alone merit an additional 3X safety factor, in addition to the currently established 10X.

HED Response

The decision to apply a 10X FQPA safety factor was based on several sources of residual concerns and uncertainty associated with exposures to the chlorotriazines. These sources of uncertainty primarily concern the hazard of atrazine and it metabolites, although there are some residual concerns in exposure database. Although the FQPA safety factor should not be parceled out among the varying concerns, but rather the concerns cited considered *in toto* and used as the basis for retaining the default FQPA safety factor.

The decision to retain the default 10X FQPA safety factor or to assign a different safety factor is

informed by the conclusions presented in the risk characterization, i.e., the final step in the risk assessment process. The risk characterization is an integration step wherein the weight-of-evidence analyses for the completeness of the toxicity database, the degree of concern for pre- and postnatal toxicity, and results of the exposure assessments are combined to evaluate whether the presumptive 10X safety factor should be retained. If there is a high level of confidence that the combination of the hazard and exposure assessments is adequately protective of infants and children, then the presumption in favor of the additional 10X default FQPA safety factor would be obviated and the FQPA safety factor is reduced to 1X. Conversely, if there is evidence that raises concern for pre- or postnatal toxicity or problems with the completeness of the toxicity or exposure databases and these uncertainties have not been adequately dealt with in the toxicity and/or exposure assessments (through use of traditional uncertainty factors or conservative exposure assumptions) then the presumptive additional 10X safety factor should be retained (see "Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Reassessment", Office of Pesticide programs, US EPA, January 31, 2002 (http://www.epa.gov/pesticides/trac/science/#10-fold).

Scientific judgment should be used in determining the appropriate size of the FQPA safety factor based on the toxicology and exposure data available for the pesticide and based on the understanding of whether the missing or inadequate data on a pesticide are likely impact to impact the risk assessment, for example by identifying new effects and effects occurring at lower doses. In the case of atrazine and its metabolites a major consideration on the toxicology side was how thorough were the data with respect to life stage and end point assessment. There was no information on atrazine concerning dosing that covered all critical developmental periods, gestation through puberty in both male and female rats, in particular dosing early in development. Such exposure might reasonably be anticipated to lead to lower NOAELs than those identified in the current studies.

Furthermore, atrazine's effects on neurotransmitters/peptides were only evaluated after acute dosing and thus there were residual concerns for longer exposures and longer doses to atrazine and its metabolites and their impact on these neurotransmitters and peptides that are known to be critical for development and normal functioning. Also, atrazine and its metabolites have not been evaluated for CNS effects, and thus there were residual concerns of whether atrazine's CNS mode of action would lead to behavioral effects in the young, and at what dose compared to its reproductive developmental effects.

It is important to note that in the case of atrazine, there are more reliable data on actual exposures to chlorotriazines in finished drinking water than for any other pesticide. In this sense, the exposure database for atrazine is particularly robust. As a result we have moderate to high confidence and there is less uncertainty in our estimates of exposure to the chlorotriazines in drinking water than for all other pesticides assessed to date. However, because of the infrequency of monitoring under the SDWA, and because data on the chlorotriazine degradates in surface water and groundwater (rural wells) are limited to a few CWS and/or wells and have been extrapolated to other CWS, i.e., data are not available for each CWS assessed as are data on the parent compound, atrazine, there is residual uncertainty regarding the full extent of exposures

to atrazine in drinking water.

In total, these residual concerns led to the decision to retain the 10X FQPA factor. An order of magnitude beyond the standard uncertainty factors (100X) is considered adequately protective of all populations including children. It is unlikely that new effects that may be potentially identified would result in NOAELs lower than an order of magnitude from the current NOAELs. Given the existing monitoring database, it is also unlikely that high-end exposures an order of magnitude greater than those already identified exist. Therefore, 10X factor is believed to be adequate given the overall toxicity database and exposure information available for atrazine and the chlorodegradates. Thus, HED believes the decision to apply a 10X FQPA safety factor is justified and adequately protective. In response to these uncertainties, the additional 10-fold safety factor for children has been applied, and studies examining CNS alterations have been recommended

Comment

Seasonal effects of atrazine in drinking water:
Several of the comments expressed concern about short-term and season-long average atrazine levels exceeding the 3 ppb MCL in drinking water. This may particularly important for assessing exposures of infants and children at critical times of development.

HED Response

Oral ingestion of atrazine residues in drinking water is the most significant exposure pathway for atrazine. OPP is keenly aware of the occurrence of peak exposures to atrazine and its chlorotriazine metabolites that exceed the MCL in the weeks to months following application in the Spring, particularly in the Midwest where atrazine is heavily used. For this reason, OPP specifically included a risk assessment for intermediate-term effects and exposures to atrazine and its chlorotriazine metabolites. This risk assessment included the attenuation of the LH surge as a biomarker for neuroendocrine effects that may be occurring in humans (adults and children) after several months of exposure as the intermediate-term effect, and a 3-month seasonal average exposure to atrazine and its chlorotriazine metabolites in drinking water for all populations including infants and children. The inclusion of this exposure scenario is specifically designed to assess the high-end seasonal exposures of infants and children to spikes of atrazine and the chlorometabolites in drinking water. It is under this specific assessment that the most significant exposures to infants and children are noted in the risk assessment. The assessment identifies specific community water systems of potential concern for infants' and children's exposures.

In the intermediate-term risk assessment, HED included exposures from Jan/Mar, Apr/Jun, Jul/Sep, and Oct/Dec. As can be seen in the revised preliminary risk assessment, the exposures of concern are for infants and children drinking water with high seasonal chlorotriazine exposures. The most recent probabilistic assessment includes 90-day rolling exposure durations that progress from Jan 1993 through December 2000 in 90-day increments for the community water systems with the highest exposures. This assessment should provide the most precise

examination of seasonal exposures to atrazine and the chlorotriazine metabolites. HED included one-day assessments of atrazine and its chlorometabolites in drinking water as well. OPP notes that the MCL of 3 ppb was established to be protective of long-term annual and multi-year exposures to atrazine, not shorter-term, seasonal exposures. The 3 ppb MCL was established when atrazine was classified as a C carcinogen (possible human carcinogen), and is based on a heart effect in the dog.

OPP also assessed short-term exposures occurring over 1-day (maximum 1-day acute exposures) based on an endpoint from developmental studies for delayed ossification in cranial bones in offspring. The endpoint is considered protective of infants and children's effects that may be occurring via high-end, 1-day, pre- and post-natal (fetal and offspring) exposures. The risk assessment determined that one-day exposures to atrazine are not of concern for the relevant population affected.

Comment

The commentary is suggesting that, for acute risk assessments, it is inappropriate to use percent crop treated information or use data that reflect a distribution of residue values. When looking at the effects that occur after only one dose or a short-term exposure, the commentary continues, risk assessment should be performed which assume that the affected persons are consuming atrazine-treated foods. The commentary goes on to say that acute risk assessments should never include any averaging of exposures over time which is what they believe using percent crop treated data does.

HED Response

These issues have been addressed by OPP before in a variety of responses to public comments, SAP reports, and policy documents. OPP believes that the use of probabilistic techniques to perform acute dietary exposure analyses allow a more realistic evaluation of exposures through food and permit the risk manager to make decisions which reflect a truer picture of risk. Older methods used by OPP for acute dietary risk assessments were limited to the assumption that 100% of the crop was treated, and the resulting acute risk estimates were considered "high end" or "bounding"; these provided little information to the risk manager on the variability or uncertainty associated with the risk estimate nor any indication of how probable such high-end exposures were or what might be more expected levels of exposure. In short, then, OPP believes that its use of probabilistic techniques in acute risk assessments are entirely appropriate and that the use of percent crop treated is an important consideration that is a critical and necessary component of any probabilistic risk assessment.

The commentary seems to be somewhat confused about how percent crop treated is used by OPP in an acute risk assessment. They state that "acute risk assessments] should never include any averaging of exposures over time, which is what using percent crop treated data does." In reality, using percent crop treated does NOT average exposures over time, but rather instead accounts for the *probability* (frequency) of an exposure occurring. More specifically, this

percent crop treated factor determines the proportion of crop that is assumed to have zero residues (calculated as 1- PCT). Probabilistic assessments as performed by OPP do not "adjust" the measured residues or average exposures over time, but rather assign a probability of encountering a residue in any individuals daily food consumption. The difference between using percent crop treated as an adjustment factor (an invalid approach) and using it as an assigned probability (a valid approach) is illustrated below:

Illustration of Valid and Invalid Means of Incorporating Percent Crop Treated (%CT) Into an Acute Probabilistic Assessment			
Invalid			Valid
Available Residue Values	%CT	Resulting Residues	90% Probability of residue being "zero"
		0.034 ppm	and
0.34 ppm	10	0.026 ppm	
0.26 ppm		0.049 ppm	10% Probability of residue being either 0.34 ppm, 0.26 ppm, 0.49 ppm, 0.86 ppm, or 0.43 ppm
0.49 ppm		0.086 ppm	
0.86 ppm		0.043 ppm	
0.43 ppm			

In an acute probabilistic exposure assessment, using the valid approach outlined above, a distribution of residue values would be constructed consisting of 45 zeros and the 5 residue values shown. This provides a 90% chance (probability) that a residue concentration of zero will occur and a 10% chance that a residue value of either 0.34 ppm, 0.26 ppm, 0.49 ppm, 0.86 ppm, or 0.43 ppm will occur in the assessment. Each of the 5 residue values shown have an equal probability relative to each other (2%) of occurring in the assessment. OPP's probabilistic assessments ensure through successive iterations that all residue values in the constructed distribution occur in the assessment. Therefore, all of the residue values available will be represented (included) in the probabilistic assessment with the appropriate frequency with which they are expected to occur in the food supply. The use of the %CT factor in the acute probabilistic assessment ensures that the available residue data are neither over-represented nor under-represented in the assessment.

Comment

Average residues, body weights and consumption patterns should not be used in the chronic dietary risk assessment. The Agency should use 99th percentile estimates of residues and consumption to protect people consuming above-average residues of atrazine. Concern was expressed that children's body weights and consumption patterns should be used in the risk assessment.

HED Response

One of the fundamentals of risk assessment is matching the appropriate toxic endpoint with the appropriate exposure duration. It would be incorrect to match a toxic endpoint for effects noted

after months or years of exposure to a one-day high-end exposure scenario. Conversely, it would also be incorrect to match a toxic endpoint noted after single, one-day exposures to typical exposures incurred over many months or years. The chronic dietary risk assessment is based on chronic dietary exposures, i.e., exposures incurred over the long-term, and a toxic endpoint believed, in the case of atrazine, to represent intermediate-to-long-term effects as a result of intermediate-to-long-term exposures. As a result, average dietary exposures are estimated based on average residues in foods, average body weights, and average consumption patterns.

OPP uses the acute dietary risk assessment to estimate risk associated with high-end, short-term (usually one-day) exposures and compared that to an appropriate endpoint for single dose effects. Under the acute risk assessment maximum individual measured residues, and individual body weights and consumption patterns are included, not averaged as in the chronic risk assessment.

OPP's dietary risk assessments include separate exposure and risk assessment for various subgroups of adult males, adult females, infants, and children. OPP uses the USDA's Continuing Survey of Food Intake by Individuals (CSFII) to represent consumption patterns and body weights as reported by consumers for all of these disparate groups. OPP does not average body weights and consumption patterns across all of these different population subgroups under the chronic dietary risk assessment. OPP does average body weights and consumption patterns within a specific population subgroup under the chronic dietary risk assessment in an effort to assess or estimate the long-term, average exposure of individuals within the population subgroups.

HED notes that dietary exposure to atrazine is insignificant whether concerned with high-end one-day exposures or long-term average exposures to atrazine and the chlorometabolites. This is largely driven by atrazine's use pattern; it is mainly used on animal feed commodities. The main dietary concern for atrazine is the presence of the chlorometabolites in milk, particularly DACT. USDA's Pesticide Data Program (PDP) analyzed 1892 milk samples in 1997-1998 for atrazine; all samples had non-detectable residues. HED, however, included estimates of atrazine and these metabolites (including DACT) in milk based on animal feeding studies because available monitoring data are for atrazine, only, in milk, and would not have detected DACT. HED believes its' dietary assessment for atrazine and the chlorometabolites is refined, but conservative and protective.

Comment

Atrazine in water may be inhaled or absorbed dermally. Shower exposures should have been included in the risk assessment. Failure to include this exposure pathway for organic solvents such as benzene and chloroform have results in a 50% underestimation of exposures to these chemicals.

HED Response

OPP acknowledges that exposures to atrazine through showering and bathing were not included in the risk assessment. Atrazine is not a volatile chemical. Inhalation exposures are not anticipated as a major exposure pathway. Atrazine has a vapor pressure of 2.89×10^{-7} mm Hg at 25 C. The vapor pressure of benzene is 94.8 mm Hg at 25 C, and for chloroform is 197 mm Hg at 25 C. The comparison of vapor pressures of atrazine to compounds like benzene and chloroform shows that benzene is 333,333,333 times more volatile than atrazine, and chloroform is 666,666,667 times more volatile than atrazine. Clearly, inhalation through volatilization is the most significant exposure pathway for benzene and chloroform. To exclude exposure via inhalation in the shower for compounds like benzene and chloroform present in tapwater would clearly be an error. It is not surprising that exposure via showering for these compounds accounts for 50% of total exposure to these compounds because of their high volatility. Equally clearly, however, given the low volatility of atrazine that is nine orders of magnitude less than organic solvents like benzene and chloroform, it can be seen that inhalation through volatilization is not a significant exposure pathway for a non-volatile, water soluble compound like atrazine.

Comment

EPA used a flawed human study for dermal absorption. The study in question used too few subjects (10) to account for variability in the population, and did not include abraded or chapped skin relevant to worker exposure, and did not include that children's skin is thinner and more permeable than adults' skin. The comment urges EPA to use the 22% dermal absorption factor from a rat study, and expresses concerns about the ethics of human testing.

HED Response

Because toxicity testing overall involves too few subjects to account for interspecies variability, OPP routinely applies a 10 uncertainty factor to all risk assessments to account for this uncertainty. The atrazine risk assessment includes the 10X uncertainty factor for interspecies variability.

OPP acknowledges that the available data indicates that skin permeability of atrazine is lower in humans than in rats. It is not uncommon for humans to have lower skin permeability to many compounds compared to rats. The stratum corneum known to absorb many compounds and serve as a reservoir of absorbed compound from which a compound steadily diffuses across the epithelium into the dermis is much thicker in rats than in the human resulting in this reservoir being a much greater factor to the rat than to the human. As a result rat dermal absorption frequently is much greater than human dermal absorption.

OPP is interested in reducing uncertainty where possible in its risk assessments. OPP uses human data to inform our risk assessments. The human dermal absorption factor was not used directly in the risk assessment as 6% in this case because the dermal endpoint came from a rat study. Instead, HED used the human dermal absorption factor in conjunction with the rat dermal absorption factor. OPP used the 22% absorption factor for rats divided by the 6% dermal

absorption factor for humans and calculated a dermal penetration factor of 3.6 for use in risk assessments involving dermal exposures. The no observed adverse effect level (NOAEL) selected for use in short-term dermal exposure assessments was 100 mg/kg/day based on reductions in mean body weight gains at 1000 mg/kg/day. This NOAEL adjusted by the dermal penetration factor of 3.6 results in a NOAEL for use in risk assessment of 360 mg/kg/day. If the human dermal absorption factor had been used directly in the risk assessment, the NOAEL used in the assessment would have been 1667 mg/kg/day.

Although workers hands are likely to be rough, cracked, chapped, or irritated, they are also likely to wear gloves as directed when handling atrazine products. Hands are clearly the single most-exposed body part for workers, and gloves as protection are essential to avoid much of the unwanted exposure.

Comment

The comments assume that EPA should be able to obtain data on residues of atrazine in animal fat below tolerance levels. EPA did not have PDP monitoring data on field corn, but had to use field trial data from the registrant to assess atrazine residues in corn. It is important to collect these data right away to make sure corn is not a significant exposure pathway.

HED Response

Unfortunately, OPP was unable to obtain this information from FSIS. When pressed to provide records HED was informed that there were none available for the following reasons. At one time FSIS did a lot of pesticide testing. They analyzed for carbamates, pyrethroids, OPs, CHC, and may even have tested for atrazine, etc. But that was back in the early to mid 1980s. At that time, however, FSIS was only giving OPP the total tested results and the results above tolerance. These old data were recorded using old computer equipment, so the raw data values from that time are virtually impossible to access anymore. Since 1992, FSIS has reported results above and below tolerance, but only tested for chlorinated hydrocarbons, a few chlorinated OPs, some benzimidazoles and avermectins. Since 1992 OPP has received data from FSIS on detections above and below tolerances, but only on a limited number of pesticides. Unfortunately, data developed since 1992 on pesticide residues in animal fats has not been available for atrazine. The older data are available for many more pesticides, but the data available only reports tolerance violations. HED recommended these data be recorded and kept; however, the commentary should feel free to express their concerns directly to FSIS regarding its record keeping practices.

Monitoring data were available from PDP and FDA on sweet corn, which is a human food commodity. Field corn is an animal feed commodity and is not regularly tested under the PDP. Sweet corn is important as an item directly consumed by humans, and field corn is important because of the potential for residue transfer through meat and milk of animals consumed by humans. Even though all sweet corn samples tested for atrazine had non-detectable residues, in an effort to conservatively estimate the residues of atrazine contributed to the human diet via

direct sweet corn consumption , HED used available plant metabolism and field trial data on field corn. This is considered reasonable because the use patterns for atrazine on sweet and field corn are identical. Field trial data tend to reflect much higher residues than monitoring data as it represents residues at the farm gate rather than the typically lower residues or foods that have been washed, stored and distributed prior to consumption. Therefore, the use of field trial data for field corn results in a more conservative estimate of residues of atrazine on sweet and field corn. Using plant metabolism data allowed estimates of atrazine residues in sweet corn tissues at very low levels otherwise undetectable because the residues were tagged with a radioactive label. Similarly, using animal metabolism data allowed estimates of atrazine residues in fat and meat and milk at very low levels otherwise undetectable because the residues were tagged with a radioactive label. Through the available data, HED has conservatively estimated residues of atrazine and the chlorometabolites in sweet corn, and meat and milk. As a result of this effort, HED has determined that dietary exposure to atrazine and the chlorometabolites is insignificant, and that corn is not a significant exposure pathway. HED has encouraged other agencies to include the chlorometabolites of atrazine in their monitoring programs for atrazine, be it for food (USDA's PDP) or drinking water (EPA's OW).

Comment

Comments were received regarding potential exposures of toddlers playing on lawns treated with atrazine. The use of the 6% dermal absorption factor from the human study is believed to underestimate dermal absorption and exposures of toddlers. Further, EPA did not consider "track-in"residues nor residues on pets that may come in contact with children. Concern was expressed that granular formulations of atrazine not be permitted on lawns in any area where toddlers play.

HED Response

As stated previously, the 6% human dermal absorption factor was not used directly in the risk assessments, but were used to inform HED's assessment, and to calculate a dermal penetration factor, a relative factor, which represents the ratio of the percent dermal absorption in rats to that of humans. This approach was taken as OPP acknowledges the difference in the absorptive capacity of rat versus human skin. HED believes that the risk assessment for toddlers playing on atrazine treated lawns are conservative because of the underlying assumptions used in these assessments conducted under the Residential SOPs (December 1999). The assessment used residue data on the day of application from turf transferable studies for granular and liquid formulations. The SOPs use a dermal transfer coefficient from a high contact activity based on Jazzercise to represent an actively playing child. These assumptions are expected to result in high-end, screening-level assessments. HED has requested a turf transferable study for granular formulations of atrazine to refine these screening-level assumptions and assessments for children's exposure to atrazine residues on lawns. The residential risk assessment has identified risks of concern for young children playing on lawns immediately after atrazine treatment. This exposure scenario of concern will be part of the risk mitigation discussions on atrazine.

Track-in and residues on pets were not included because these sources of residues represent levels of concentrations orders of magnitude lower that the exposure scenarios assessed in the residential risk assessments for incidental oral, and dermal exposures of young children. These assessments represent the most significant exposure pathways for young children exposed to residues of atrazine through registered residential uses. As stated above, conservative assumptions considered screening-level have been used to estimate exposures and risks for these exposure scenarios and are considered protective.

Comment

Atrazine and nitrates may combine to form N-nitrosoatrazine under acidic conditions in soils and in the stomach. N-nitrosoatrazine is believed to be a mutagen on human lymphocytes and may be related to non-Hodgkin's lymphoma. It should be included in the risk assessment

HED Response

HED appreciates the seriousness of this comment, and acknowledges that N-nitrosoatrazine has not been included in the risk assessment for atrazine. OPP focused the atrazine risk assessment on the significant known hazards (endocrine disruption) and exposure pathways (drinking water) associated with atrazine for which reliable exposure data were available. In particular, OPP was careful to incorporate the chlorometabolites into the assessment, and considered them to be of equivalent toxicity to the parent compound.

Since N-nitrosoatrazine can be formed *in vitro* when atrazine and nitrite are mixed at an acid pH (Wolfe, et al., 1976), and because atrazine and nitrites can occur together in drinking water, it has been hypothesized that it is possible that N-nitrosoatrazine could be formed at acid pH in the stomach. However, formation of N-nitrosoatrazine *in vivo* has not been demonstrated. N-nitrosoatrazine has been shown to be mutagenic in genotoxicity tests, but cancer bioassays in female mice and rats failed to show a carcinogenic response following N-nitrosoatrazine exposure (Weisenberger, 1990 - abstract). OPP intends to explore the extent of this compound's presence in drinking water with the OW and the registrant.